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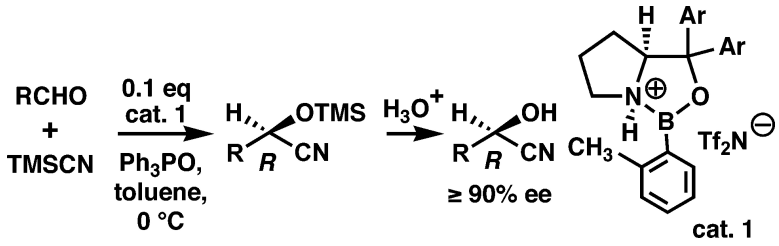

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Highly Enantioselective Cyanosilylation of Aldehydes Catalyzed by a Chiral Oxazaborolidinium Ion

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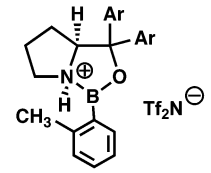
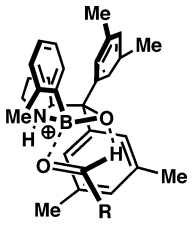
The enantioselective synthesis of cyanohydrins from aldehydes and ketones represents a useful avenue for the synthesis of important organic intermediates, for example, α-hydroxy acids and their derivatives and β-amino alcohols. For this reason there has been intense research activity in this area in recent years,[1] leading to the development of a large and diverse array of chiral catalysts. Although a few of these catalysts are purely organic, metal-free reagents,[2] the majority consist of chiral ligands attached to metals such as Mg,[3] Al,[4] Ti,[5] Y,[6] Zr,[7] and Gd.[8] Despite extensive investigation, the ideal catalytic system for the practical and broadly applicable synthesis of cyanohydrins remains elusive. Furthermore, even in the cases where good enantioselectivities can be obtained there is still great uncertainty regarding the mechanistic reasons for absolute stereocontrol, an ironic situation considering that the mechanism of classical cyanohydrin synthesis was one of the earliest to be elucidated unambiguously.[9] In this paper we describe a new chiral catalyst system that is based on boron and the recognition of a novel cyanide donor. A variety of aldehydes, aromatic and aliphatic, have been transformed into cyanohydrins with >90% enantiomeric purity under standardized conditions. The chiral precursor of the catalyst is readily recoverable. Finally, the absolute stereochemical course of the reaction is predicted clearly by a well-precedented mechanism.



1, Ar = 3,5-dimethylphenyl (mexyl)

2, Ar = phenyl



3

The boron catalyst employed in this research on enantioselective cyanosilylation is the oxazaborolidinium bistriflimidate **1**, a powerful chiral Lewis acid that has recently been employed in these laboratories for a wide range of highly enantioselective Diels–Alder reactions.[10] There is much evidence in support of the formation of complexes between **1** and aldehydes that can be formulated in three dimensions as **3**.[10,11] Several key features of structure **3** suggested its use for the enantioselective cyanosilylation of a coordinated aldehyde, RCHO: (1) nucleophilic attack on the formyl carbon should be facilitated by complexation and should occur at the *si* (front) face because of shielding of the opposite (rear) face by the neighboring π-electron-rich *m*-xylyl (mexyl) ring and (2) structure **3** is fixed with regard to rotation about the coordination link between B and O by a cooperative C–H···O hydrogen bond.[11] These ideas lead to the expectation that use of catalyst **1** for the cyanosilylation of an aldehyde should produce preferentially the silylated (*R*)-cyanohydrin.

A second aspect of the new methodology described herein emerged from the study of a curious finding by Shibasaki and co-workers in connection with their recent work on enantioselective cyanohydrin formation using various chiral Ti and Al complexes. These workers found that enantioselectivities were sometimes enhanced by the addition of "promoters" such as Bu_3PO, $CH_3P(O)Ph_2$[4a,12,13] and Ph_3PO.[14,15] These phosphine oxide activation effects led to the incorporation of phosphine oxide moieties into the catalytic Lewis acid structures as a Lewis acid-Lewis base pair for what has been described as "two-center catalysis."[1c] We suspected that these effects might be the result of a reaction between the phosphine oxide and trimethylsilyl cyanide (TMSCN) as follows:

$$Ph_3PO + TMSCN \rightleftharpoons Ph_3P(OTMS)(N{=}C{:})$$

4

Support for this idea was obtained by a few simple NMR experiments. When a 1:1 mixture of TMSCN and Ph_3PO in $CDCl_3$ at 23 °C was monitored by ^1H NMR, the development of a new TMS peak at 0.05δ was observed (TMSCN peak at δ 0.36). The ^{13}C NMR spectra (in $CDCl_3$) also changed, with new peaks appearing at δ 1.84 and 110.1 (TMSCN peaks at δ −1.92 (CH_3) and 127.1 (CN)). Further, the IR spectrum of the mixture showed a new NC stretching band at 2072 cm^{-1}, different from TMSCN (2192 cm^{-1}) and TMSN=C (2095 cm^{-1}).[16] In the presence of a catalytic amount of the oxazaborolidinium ion **2** (Ar = C_6H_5), the development of the new peaks was dramatically accelerated and equilibrium was attained within a few minutes at 0 °C in toluene-d_8. ^{31}P NMR analysis revealed that the new product contained phosphorus and showed a peak at δ 28.77 as compared to δ 28.24 for Ph_3PO. Taken together, these data demonstrate a reaction between Ph_3PO and TMSCN and suggest the possible formation of isocyanide **4** as a reactive intermediate that could explain the previous results.[4a,12−15] With 0.2 M Ph_3PO and 0.4 M TMSCN, the ratio of TMSCN to **4** was measured to be 2.2:1 at 0 °C in toluene-d_8. The infrared data suggest the isocyanide structure for **4**. Although this point requires confirmation, it is clear that the isocyanide form of **4** would be the more reactive as a cyanosilylation reagent than the isomeric cyanide.

Initial experiments on the reaction of benzaldehyde with TMSCN in toluene at 0 °C in the presence of 0.1 equiv of catalyst **1** showed that excellent yields and enantioselectivity (ca. 40:1) of cyanation product could be obtained in the presence of 0.2 equiv of Ph_3PO. In contrast, under the same conditions but without any added Ph_3PO the cyanation product was formed with only low enantioselectivity. Table 1 shows the results of cyanation experiments with a variety of aldehyde substrates under essentially optimal conditions with 0.2 equiv of Ph_3PO to generate the reactive intermediate **4**. Both the yield and enantiomeric purity of isolated cyanohydrin are

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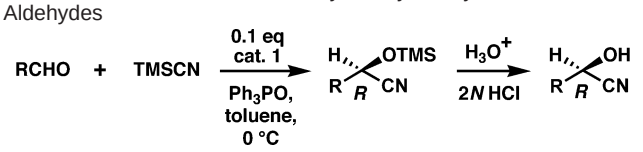
Table 1. Oxazaborolidinium-Catalyzed Cyanosilylation of Aldehydes



R	time, h	% isolated yield	% ee[a,b]
phenyl	40	94	95
2-tolyl	72	95	91
4-anisyl	40	91	90
4-cyanophenyl	144	98	97
cyclohexyl	40	97	90
tert-butyl	40	96	91
n-hexyl	48[c]	96	91

[a] Enantioselectivities determined by GC or ^{1}H NMR analysis of cyanohydrins. [b] Performed using 0.2 equiv of Ph_3PO. [c] Reaction temp = −20 °C.

excellent in each case, and the scope of the process includes not only a range of substituted aromatic aldehydes but also a variety of α-substituted aliphatic aldehydes. In each case, the initial product is the TMS ether of the cyanohydrin, which can readily be isolated or transformed into cyanohydrin by mild acidic hydrolysis. Enantioselectivities were determined either by gas chromatographic analysis or ^{1}H NMR analysis of the Mosher (MTPA) ester of the cyanohydrin using established analytical protocols.[1−8]

There are advantages to the methodology besides the excellent yields and enantioselectivities displayed in Table 1. The catalytic ligand is easily and efficiently recoverable for reuse (ca. 96% recovery yield of (*S*)-dimexylpyrrolidinomethanol). The cyanosilylation is easily scalable since it is homogeneous and generally can be carried out at 0 °C. Obviously, on a scale larger than that used for these initial investigations (1−5 mmol at 0.2−0.4 M concentration of RCHO), even higher concentrations of reactants can be used so as to diminish reaction times.

Although we have not carried out exhaustive investigations to find the optimal phosphine oxide-type coreactant, studies thus far indicate that Ph_3PO is distinctly superior to any of the following: $(EtO)_3PO$, $(2\text{-furyl})_3PO$, $(4\text{-F-phenyl})_3PO$, Ph_3PS, Ph_2SO. With regard to Ph_3PO as a coreactant, it should be mentioned that it affects the reaction rate in two opposing ways. Since Ph_3PO is a Lewis base, it competes with RCHO for coordination with the oxazaborolidinium cation and thereby retards the cyanosilylation reaction. This effect is clear from the study of reactions other than cyanosilylation that are catalyzed by **1**, for example, enantioselective Diels−Alder additions. Thus, although the [4 + 2]-cycloaddition reaction of 2-methylacrolein and isoprene at −78 °C in the presence of 10 mol % **1** is complete within 1 h, there is hardly any reaction under the same conditions if 2 equiv of Ph_3PO are present per equiv of **1**. On the other hand, the formation of the reactive intermediate $Ph_3P(OSiMe_3)NC$ clearly must accelerate the cyanosilylation process.

Although most of our experiments have been carried out with the mexyl-substituted catalyst **1**, we have also examined the use of the diphenyl analogue **2** with several of the substrates listed in Table 1. In general, the two catalysts are essentially equivalent, but in a few cases the ees observed for the cyanohydrin product were 1−2% lower with **2** as compared to **1**.

In conclusion, we believe that the results summarized in Table 1 recommend the use of the methodology for enantioselective cyanosilylation that is described herein. It is gratifying that, in all cases studied so far, the absolute configuration of the cyanohydrins produced is that predicted by **3** and the mechanistic model. Further investigations are planned to provide additional information with regard to scope, optimal coreactant, and optimal oxazaborolidinium catalysts (for instance, with regard to the substituent on boron).

Supporting Information Available: Procedures for cyanosilylation and also characterization and analytical data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The following general procedure was developed. *CAUTION: TMSCN is volatile and toxic and must only be used in a well-ventilated hood.* A solution of catalyst **1** (0.5 mmol in 7.5 mL of toluene; for preparation see Supporting Information or ref 10e) was added to 293 mg (1.0 mmol) of Ph_3PO with stirring under N_2. Then, TMSCN (0.752 mL, 5.64 mmol) was added followed by the aldehyde (5 mmol, dropwise) in 3−5 mL of toluene over 1 h at 0 °C. After the reaction time indicated in Table 1, the reaction mixture was concentrated in vacuo, and 5 mL each of water and pentane were added. Extractive workup provided essentially pure cyanohydrin TMS ether from which cyanohydrin was obtained by stirring with 5 mL of 2 N HCl and 5 mL of EtOAc, isolation from the EtOAc layer, and passage through a column of silica gel.

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